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INTERLEUKIN-1 SIGNALLING INHIBITORS IN HEART FAILURE WITH PRESERVED AND REDUCED EJECTION FRACTION

<i>Aim</i>	To assess circulating levels of interleukin 1 (IL-1), soluble IL-1 receptor type II (sIL-1R2) and IL-1 receptor antagonist (IL-1Ra) in patients with heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) in acute decompensated heart failure (ADHF) and in stable condition.
<i>Material and methods</i>	The study included 42 patients with HFpEF and 117 patients with HFrEF admitted for ADHF. After 12 months of follow-up, 31 patients with HFpEF and 84 patients with HFrEF were re-examined. Their condition was assessed as clinically stable. Plasma concentrations of IL-1, IL-1R2, and IL-1Ra were measured in all patients.
<i>Results</i>	In ADHF, IL-1R2 and IL-1Ra concentrations were higher than in stable condition, with IL-1Ra concentrations increasing markedly (3.5 times). Depending on the left ventricular ejection fraction, IL-1 was lower in patients with HFpEF, while IL-1R2 and IL-1Ra were higher than in patients with HFrEF. IL-1 was not detected in stable condition, and differences in IL-1R2 and IL-1Ra concentrations between fractions subsided.
<i>Conclusion</i>	In ADHF, the differences in the concentrations of IL-1 and endogenous inhibitors of IL-1 signaling, IL-1R2 and IL-1 β Ra, in patients with HFpEF and HFrEF indicated different severity of the inflammatory response in these fractions and more intense neutralization of IL-1 in patients with HFpEF compared to patients with HFrEF, which should be taken into account in the therapeutic blockade of IL-1.
<i>Keywords</i>	Acute decompensated heart failure; interleukin-1; interleukin-1 receptor type II; interleukin-1 receptor antagonist; left ventricular ejection fraction
<i>For citations</i>	Samoilova E. V., Chepurnova D. A., Nasonova S. N., Zhironov I. V., Tereschenko S. N., Korotaeva A. A. Interleukin-1 Signalling Inhibitors in Heart Failure With Preserved and Reduced Ejection Fraction. <i>Kardiologiia</i> . 2025;65(11):67–70. [Russian: Самойлова Е. В., Чепурнова Д. А., Насонова С. Н., Жиров И. В., Терещенко С. Н., Коротаева А. А. Эндогенные ингибиторы сигнализации интерлейкина-1 при сердечной недостаточности с сохраненной и сниженной фракцией выброса левого желудочка. <i>Кардиология</i> . 2025;65(11):67–70].
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Introduction

Patients with chronic heart failure (CHF) remain at high risk of adverse outcomes despite groundbreaking medical advances. The course of CHF is cyclical and characterized by episodes of stability interspersed with episodes of aggravation of clinical symptoms. An episode of acute decompensated heart failure (ADHF) is particularly unfavorable and requires urgent medical attention and emergency admission. Each episode of ADHF negatively affects the course of CHF and increases the risk of death. The pathophysiology of ADHF is multifaceted and depends on many factors, including the degree of left ventricular systolic and diastolic dysfunction and the activation of inflammation [1]. Inflammation is known to play an important role in the development and progression of CHF [2]. Cytokines actively participate in the inflammatory process and influence its severity. The course of inflammation largely depends on the activity of endogenous anti-inflammatory mechanisms. Interleukin-1 (IL-1) ini-

tiates the inflammatory process and regulates its intensity and duration by triggering the cytokine cascade. A natural inhibitor of IL-1 signaling is the IL-1 receptor antagonist (IL1Ra) that competitively binds the membrane receptor and interrupts the signal transduction [3]. The balance between IL-1 and IL1Ra concentrations modifies physiological and pathophysiological effects of IL-1, and a disruption of this balance contributes to the development and severity of many diseases [4]. Furthermore, the IL-1 receptor type II (IL1R2) participates in the negative regulation of IL-1 signaling by acting as an IL-1 trap and potentially influencing the course of diseases [5].

Aim

To determine and compare circulating levels of IL-1, IL1R2, and IL1Ra in patients with heart failure with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) of the left ventricle in ADHF and in stable condition.

Material and methods

The study included 159 patients admitted for ADHF. HFrEF (<40%) was diagnosed in 117 patients, and HFpEF (≥50%) in 42 patients (Table 1). In all cases, this parameter was determined using the Simpson method. After 12 months of follow-up, 115 patients were re-examined, including 31 patients with HFpEF and 84 patients with HFrEF. Their condition was assessed as clinically stable.

The study was performed in consistency with the principles of the Declaration of Helsinki and approved by the ethics committee of the Academician E. I. Chazov National Medical Research Center of Cardiology of the Ministry of Health of Russia (protocol #287 dated February 20, 2023). All patients signed informed consent to participate in the study. The study did not include patients with malignant neoplasms, left ventricular outflow tract obstruction, restrictive heart diseases, severe kidney or liver dysfunction, and clinically significant acute and chron-

ic inflammatory diseases requiring specific therapy that could potentially affect the studied parameters.

Venous blood samples were collected upon admission and after a year of follow-up. Before the study, plasma samples were stored at -80 °C.

The concentrations of IL-1, IL1R2, and IL1Ra were measured by enzyme immunoassay using MyBioSource (USA) reagent kits.

Statistical analysis was performed using an IBM SPSS Statistics 23.0 software package. The results are presented as median with interquartile range (Me [Q1; Q3]) for variables with a distribution different from normal. Statistically significant differences between quantitative variables of two independent samples with a non-normal distribution were identified with the Mann-Whitney U-test; significant differences between quantitative variables of two related samples were identified with the Wilcoxon test. Statistically significant differences between qualitative variables in two independent samples were identified

Central illustration. Endogenous inhibitors of interleukin-1 signaling

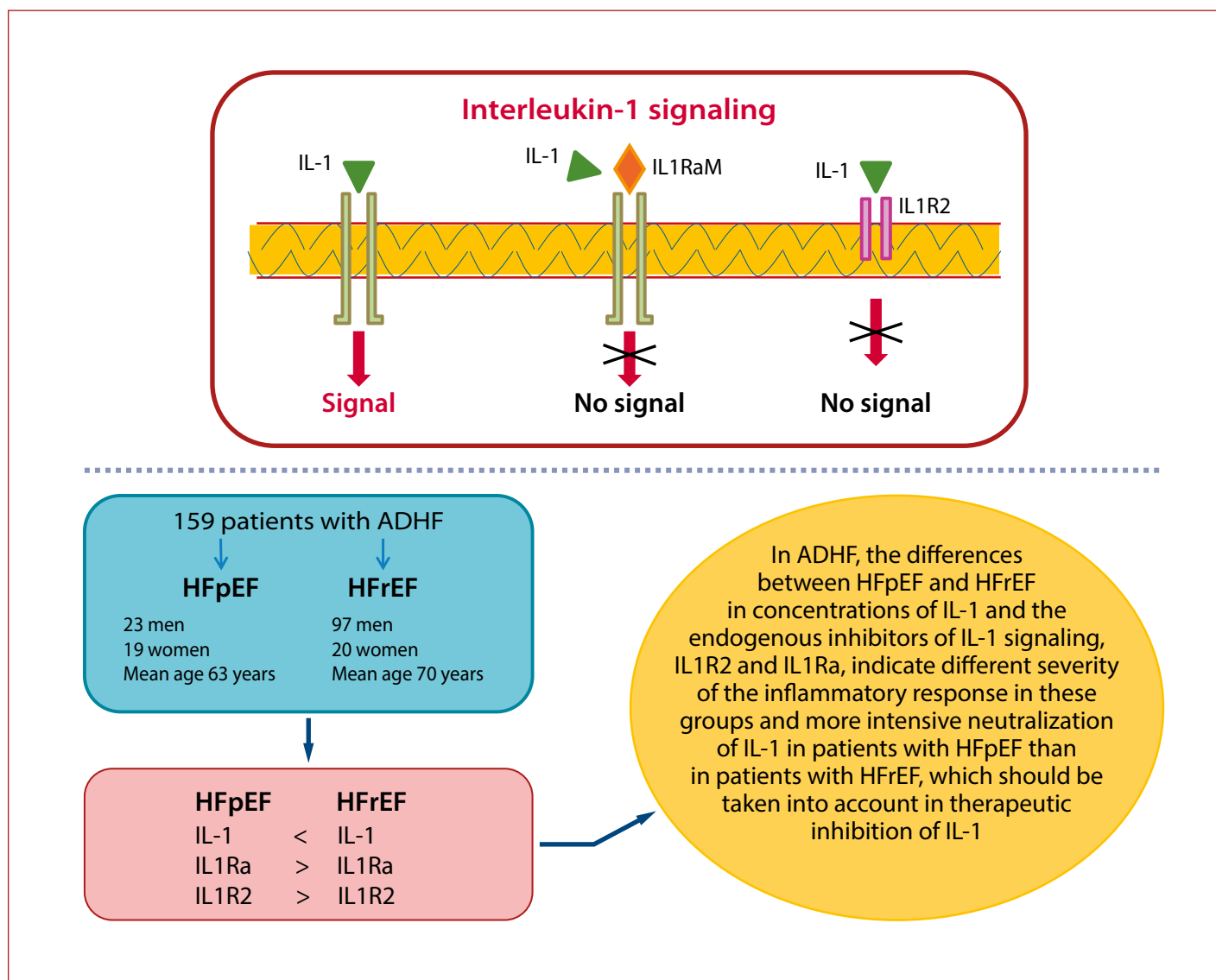


Table 1. General characteristics of patients with ADHF depending on left ventricular ejection fraction

Variable	HFpEF (n=42)	HFrEF (n=117)
Age, years (Me [Q1; Q3])	63 [55; 70]	70 [64; 77]
Gender (male/female), n (%)	23 (55) / 19 (45)	97 (83) / 20 (17)
Body mass index, kg /m ² Me ([Q1; Q3])	33 [28; 37]	29 [25; 34]
Smoking, n (%)	11 (26)	57 (48)
Arterial hypertension, n (%)	36 (86)	77 (66)
Ischemic heart disease, n (%)	13 (31)	67 (57)
Myocardial infarction, n (%)	11 (26)	63 (54)
Diabetes mellitus, n (%)	13 (31)	33 (28)

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Table 2. Concentrations of IL-1, IL1R2 and IL1Ra in patients with ADHF and in stable condition

Variable	ADHF (n=159)	Stable condition (n=115)	p
IL-1, pg/ml	4.15 [2.70; 6.82]	ND	–
IL1R2, pg/ml	19 321.23 [15 155.20; 24 413.83]	16 955.37 [13 894.07; 21 697.75]	0.057
IL1Ra, pg/ml	653.17 [367.15; 981.28]	185.58 [101.34; 304.01]	<0.01

The data are presented as Me [Q1; Q3]. ND, not detected. ADHF, acute decompensated heart failure; IL-1, interleukin-1; IL1R2, interleukin-1 receptor type II; IL1Ra, interleukin-1 receptor antagonist.

Table 3. Concentrations of IL-1, IL1R2, and IL1Ra in patients with ADHF and in stable condition, depending on left ventricular ejection fraction

Variable	ADHF		p
	HFpEF, n=42	HFrEF, n=117	
IL-1, pg/ml	2.25 [1.66; 4.04]	4.27 [2.11; 6.75]	0.156
IL1R2, pg/ml	21644.79 [17354.04; 25536.41]	18261.96 [14333.40; 24035.36]	0.180
ILRa, pg/ml	789.19 [519.04; 1118.64]	614.45 [315.14; 966.77]	0.042
	Stable condition		
	HFpEF, n=34	HFrEF, n=81	
IL1R2, pg/ml	18347.51 [12790.24; 28137.75]	16648.76 [13991.86; 20105.59]	0.128
ILRa, pg/ml	244.82 [128.93; 300.18]	174.96 [92.92; 312.20]	0.316

Data are presented as Me [Q1; Q3]. IL-1, interleukin-1; IL1R2, interleukin-1 receptor type II; IL1Ra, interleukin-1 receptor antagonist; ADHF, acute decompensated heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

with Pearson's chi-squared test and Fisher's exact test. Results were considered statistically significant at $p < 0.05$.

Results

The concentrations of IL-1 and IL-1 signaling inhibitors were measured in ADHF patients and in stable condition. IL-1 concentrations were detected only in patients with ADHF. In stable condition, plasma IL-1 was not detected. The concentrations of IL1R2 and IL1Ra were higher in ADHF than in stable condition, with IL1Ra levels were considerably (3.5 times) increased (Table 2). This may indicate a more pronounced immune response in ADHF.

Comparing patients with different left ventricular ejection fractions showed that IL-1 levels were lower in ADHF patients with HFpEF than in ADHF patients with HFrEF, while IL1R2 and IL1Ra concentrations, conversely, were higher in patients with HFpEF than in patients

with HFrEF. These differences disappeared after stabilization of the patient's condition (Table 3).

Discussion

IL-1 affects virtually all tissues and systems of the body. Excessive and prolonged production of IL-1 contributes to damage to cardiomyocytes and triggers mechanisms of myocardial remodeling. Elevated blood concentrations of IL-1 in patients with ADHF are associated with death within one year after hospitalization [6]. We did not detect high concentrations of IL-1. This may be due to the fact that IL-1 binds to various plasma proteins, such as IL1R2, alpha-2 macroglobulin, and components of the complement system. The low dissociation rate of the resulting complexes may lead to a significant decrease in the measured concentration of IL-1. Normally, blood plasma contains approximately 100 pmol/L of IL1R2. This concentration reduces the detectability of IL-1 in

clinical samples by 50% [7]. In addition, IL1R2 can suppress the formation of the active form of IL-1 from its precursor, which may also affect the circulating concentrations of IL-1 [5].

The cause of HFrEF is known to be mechanical damage to the myocardium that leads to its remodeling, while HFpEF is characterized by low-grade systemic inflammation affecting the myocardium [8]. Therefore, the concentrations of inflammatory markers may differ in patients with HFrEF and HFpEF. In this study, it was interesting to note that in patients with HFpEF who had chronic inflammation, IL-1 concentrations were lower than in patients with HFrEF. IL-1 is an inflammatory mediator, and its concentrations reflect the severity of the inflammatory response. Lower concentrations of IL-1 in ADHF may be a sign of a moderate adaptive response in patients with HFpEF compared to a powerful inflammatory response in patients with HFrEF. This assumption is supported by previous reports that in ADHF, the concentrations of another inflammatory marker, interleukin-6, were also lower in patients with HFpEF than in patients with HFrEF [9].

Both IL1R2 and IL1Ra negatively regulate the IL-1 activity, but through different mechanisms. IL1R2 acts as a molecular trap by binding to IL-1 with high affinity. IL1Ra is an IL-1 antagonist and exhibits greater affinity for the membrane receptor than IL-1. By competitively binding to the membrane receptor, IL1Ra interferes with

IL-1 signaling [10]. Elevated concentrations of IL1R2 and IL1Ra may contribute to more intense neutralization of IL-1 in patients with HFpEF compared to those with HFrEF.

Study limitations

A major limitation of the study is the small number of patients with HFpEF.

Conclusion

Our data showed that in patients with acute decompensated heart failure, the concentrations of interleukin-1 and its endogenous signaling inhibitors differ depending on whether the left ventricular ejection fraction is preserved or reduced. This indicates a different degree of inflammatory response in heart failure with preserved and reduced left ventricular ejection fraction. Currently, interleukin-1 inhibition is being investigated as a new approach to treating patients with heart failure. Our results suggest that anti-inflammatory therapy will differ in heart failure with preserved and reduced left ventricular ejection fraction.

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